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Toxicity Assessment of Afatinib as Subsequent Line Therapy after Disease Progression On or After Platinum based Therapy in Recurrent, Unresectable, Locally Advanced or Metastatic HNSCC Patients - Retrospective Observational Study

Dr. Yashashree Limje[1], Dr. Praghnya Tejale[2], Dr. Ashok Kumar Diwan[3], Dr. Vijay Kumar Mahobia[4]

Junior Resident, Department of Radiation Oncology, Government Medical College and Hospital, Nagpur
Email: *limjeyashashree85[at]gmail.com*

Assistant Professor, Department of Radiation Oncology, Government Medical College and Hospital, Nagpur
Email: *drpraghnyatejale[at]gmail.com*

Professor and Head, Department of Radiation Oncology, Government Medical College and Hospital, Nagpur
Email: *tinuad76[at]gmail.com*

Associate Professor, Department of Radiation Oncology, Government Medical College and Hospital, Nagpur
Corresponding Author Email: *drvijay_mahobia[at]yahoo.com*

Abstract: ***Background: Patients with recurrent or metastatic squamous - cell carcinoma of the head and neck (HNSCC) progressing after Platinum based regimens have a poor prognosis and few treatment options. Afatinib is an irreversible ERBB family blocker, has shown efficacy in this setting. Objective: To assess the toxicity profile, safety and progression free survival of Afatinib in patients with recurrent, unresectable or metastatic or progressing on Platinum based therapy in squamous - cell carcinoma of the head and neck (HNSCC). Methods: This was a retrospective observational study conducted at a tertiary care center in Central India.50 HNSCC patients with recurrent, unresectable or metastatic cancer were continued until progression or development of unacceptable adverse events. Results: The study showed that half of the patients remained progression - free at the last follow - up. The most common grade 3 adverse events (AE) were diarrhoea (8%) and fatigue (2%). Most of the adverse events were restricted to Grade 1 and Grade 2. Conclusion: Afatinib showed predictable toxicity in squamous - cell carcinoma of the head and neck (HNSCC0 patients and are manageable with appropriate dose adjustments. Afatinib is an effective alternative post platinum failure with appropriate monitoring and have longer progression free survival.***

Keywords: HNSCC, Afatinib, metastatic, unresectable, platinum - based therapy

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) include cancers localized in the oral cavity, oropharynx, hypopharynx, and larynx. HNSCC is one of the most common cancers worldwide, with annual incidence estimated about 750000 new cases, and mortality rate accounts for 365000 new deaths worldwide in GLOBOCAN 2022. Approximatively 60% of the patients present with locoregional advanced - stage disease at diagnosis. (1)

HNSCC are generally associated with tobacco and alcohol consumption, and human papillomavirus (HPV) identified in up to 30 - 35% of the Head and neck squamous cell carcinoma (HNSCC) (mainly oropharyngeal) patients emerged as a significant factor in disease etiology and outcomes [2, 3]. The estimated 5 - year overall survival (OS) in Head and neck squamous cell carcinoma (HNSCC) patients is approximatively 50%. Differences in prognosis are reported according to tumour location, histology, T and N stages, surgical margins and nodal status, perineural/lymphovascular invasion, and for oropharyngeal cancers, HPV status. The UICC TNM 8th edition refined locally advanced diseases as either stage III or IV oral cavity, larynx, hypopharynx and p - 16 - negative oropharyngeal cancer, or T3 - 4/N0 - 3 and T0 - 4/N1 - 3 HPV - positive oropharyngeal cancer. For patients with advanced Head and neck squamous cell carcinoma (HNSCC), multimodal treatment approaches include surgery and adjuvant chemoradiotherapy (CRT) or CRT alone in patients unresectable or with poor anticipated functional outcome. CRT in resected HNSCC patients aims to decrease the risk of locoregional recurrence. Indeed, around 50% of the patients with locally advanced Head and neck squamous cell carcinoma (HNSCC) will recur at local/regional or distant sites after primary treatment. (1)

Currently, the most common first - line treatment option for early stage head and cancer is surgery followed by CTRT. And for recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) is platinum and taxanes based chemotherapy, which, in some regions including the United States and European Union, can be combined with the epidermal growth factor receptor (EGFR) - targeted monoclonal antibody cetuximab. However, ~50% of patients relapse after first - line therapy and prognosis for these patients is particularly poor. Second - line treatment options are limited but commonly include methotrexate, taxanes, and

re - challenge with platinum - based chemotherapy. More recently, the immunotherapy agents nivolumab and pembrolizumab are approved in some countries, but response rates to these agents as second - line treatment remain low and many patients, particularly those in Asian countries, cannot access such treatments. Furthermore, recent data indicate that immunotherapy agents are likely to be increasingly used in the first - line rather than second - line setting. Consequently, alternative second - line treatment options are needed. (2)

The feasibility of targeting the EGFR in Head and neck squamous cell carcinoma (HNSCC) was first demonstrated with cetuximab, and encouraging results have been observed with the oral irreversible ErbB family blocker, afatinib, in a second - line setting. (2) In the Phase III LUX - Head and Neck 1 trial (LH&N1; NCT01345682), afatinib, an oral irreversible ErbB family blocker, significantly improved progression - free survival (PFS) compared with methotrexate as second - line treatment for patients with recurrent/metastatic (R/M) HNSCC who had progressed on or after platinum - based therapy. PFS was improved with afatinib in the overall study population (median 2.6 versus 1.7 months, hazard ratio [HR]: 0.80 [95% confidence interval (CI): 0.65–0.98], p = 0.030) and across most patient subgroups, particularly in patients who had not previously been treated with an epidermal growth factor receptor (EGFR) - targeted antibody. (3)

The treatment adherence rate with afatinib in LH&N1 (89% of patients took ≥80% of the assigned afatinib treatment) was encouraging given the generally poor adherence to oral anticancer treatment in this setting. (3) This was likely, in part, owing to the predictable and manageable safety profile of afatinib. With this rationale, the study aims to assess toxicities and Progression Free Survival related to use Afatinib.

Aims and Objectives

To evaluate the toxicity profile and progression - free survival (PFS) associated with Afatinib in patients with recurrent, unresectable, locally advanced, or metastatic head and neck squamous cell carcinoma (HNSCC) following progression on or after platinum - based therapy.

2. Material and methods

Study Design

This is a **retrospective observational study** conducted at Department of Radiotherapy at a tertiary care center in Central India.

Study Population and Sample Size

The study population comprises histologically confirmed squamous cell carcinoma of oral cavity, oropharynx, hypopharynx or larynx that was recurrent, metastatic or progressed on platinum - based therapy. The study included 50 patients with head and neck squamous cell carcinoma (HNSCC).

Inclusion criteria for study:

1) Age >18 years
2) Both male and female patients
3) Histologically confirmed squamous cell carcinoma
4) Eastern Cooperative Oncology Group (ECOG) performance status 0 to 3
5) Stage III or IV locally advanced disease
6) Patients with recurrent, metastatic disease or progression after platinum - based therapy, not amenable to salvage surgery or radiotherapy
7) Primary tumour located in the oral cavity, oropharynx, hypopharynx, or larynx

Exclusion criteria for study:

1) Primary tumor site in the nasopharynx, paranasal sinuses, or salivary glands
2) Clinically significant cardiovascular abnormalities
3) Pre - existing interstitial lung disease
4) Abnormal coagulation profile
5) Abnormal liver function tests (LFT), kidney function tests (KFT), or complete blood count (CBC)

Ethical considerations

- Approval was taken from the Institutional Ethics Committee (IEC).
- Title and synopsis approved from Institutional Ethics Committee on 29/04/2025.
- The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Data Collection Parameters

1) Baseline Demographic and Clinical Data

The following variables were recorded:

- Age
- Gender
- ECOG Performance Status (PS)
- Stage at initial diagnosis
- Type of recurrence: Local / Regional / Distant metastasis

2) Adverse Events Assessment

Treatment - related adverse events will be assessed and graded. The following adverse effects will be evaluated:

- Diarrhoea
- Skin Reaction/Dermatitis
- Fatigue
- Paronychia
- Nausea
- Vomiting
- Epistaxis

Intervention given

Dose: Tab Afatinib 40mg OD PO monthly. Administer on an empty stomach (1 hr before or 3 hrs after meal)

Statistical Analysis - Data analysis was done using Microsoft Excel 2019.

Primary Outcome

Toxicity Profile

Secondary Outcome

- Progression - Free Survival (PFS):
- PFS was analyzed using the **Kaplan - Meier survival method**.

- Baseline demographic, clinical characteristics and adverse events:
- **Continuous variables:** Summarized as mean with standard deviation.
- **Categorical variables:** Summarized in terms of proportion, frequency and percentage.

3. Results

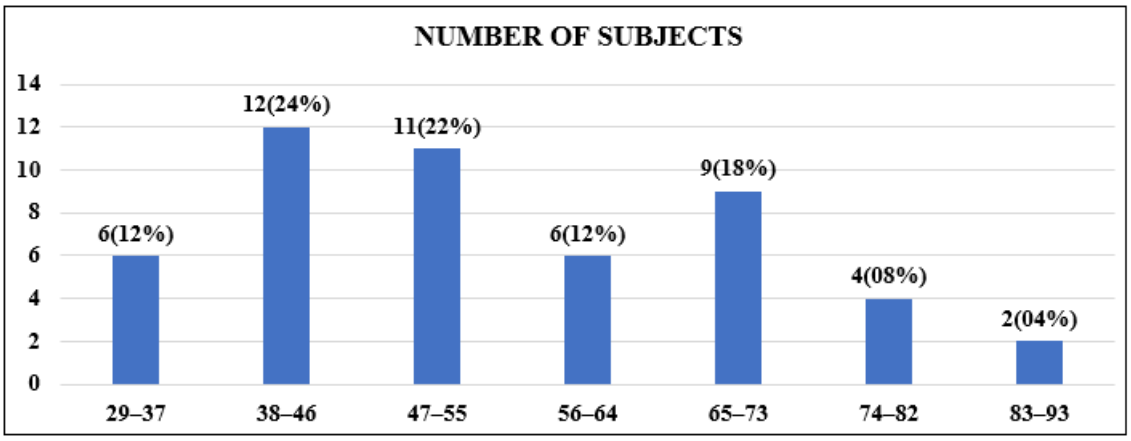

Figure 1: Distribution of study subjects according to Age

Mean + SD– 54.24 (2.14) years

Figure 01: The above figure shows the distribution of study subjects according to their age. In the present study, a total of 50 subjects were included. Majority of the study participants, 12 (24.0%), belonged to the age group of 38–46 years, followed by 11 (22.0%) participants in the 47–55 years age group. Subjects in the age group of 65–73 years constituted 9 (18.0%), while 6 (12.0%) each were in the 29–37 years and 56–64 years age groups. The 74–82 years age group included 4 (8.0%) participants. Only 2 (4.0%) participants belonged to the 83–93 years age group. This distribution indicates that the majority of the study participants were in the middle age groups of 38–55 years.

Table 2: Distribution of study subjects according to Gender

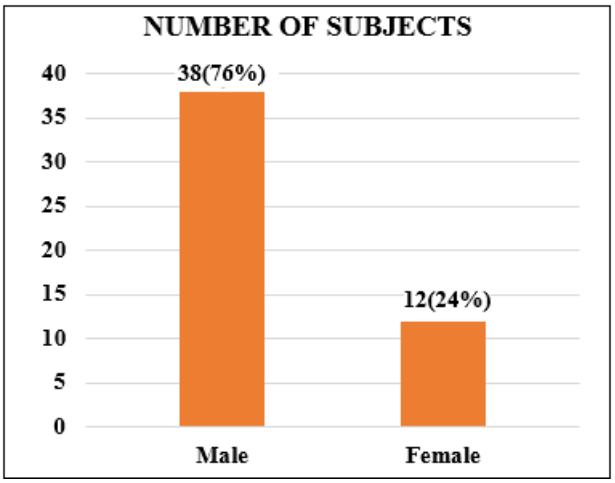

Figure 2: The above figure shows the distribution of study subjects according to their gender. The majority of the study participants were male, accounting for 38 (76.0%), while 12 (24.0%) were female.

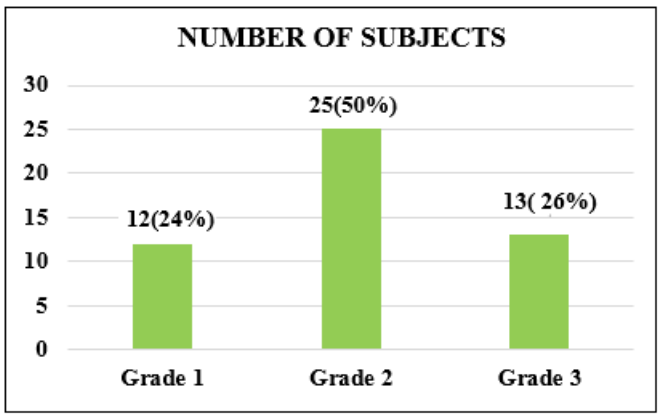

Figure 3: Distribution of study subjects according to ECOG

Figure 3: The above figure shows the distribution of study subjects according to their ECOG performance status. The majority of the study participants, 25 (50.0%), were classified as Grade 2. This was followed by 13 (26.0%) participants in Grade 3, and 12 (24.0%) in Grade 1.

Table 1: Distribution of study subjects according to Stage of disease

Stage of Disease	Number of Subjects	Percentage
ORAL CAVITY		
T3N2bM0	1	2%
T3N3bM0	1	2%
T4aN0Mx	1	2%
T4aN0M0	2	4%
T4aN1Mx	2	4%
T4aN1M0	4	8%
T4aN1M1	2	4%
T4aN2cMx	2	4%
T4aN2M0	1	2%
T4aN2cM0	3	6%
T4aN3bMx	1	2%
T4aN3bM0	1	2%
T4bN0M0	1	2%
T4bN1M1	2	4%
T4bN2bMx	1	2%
T4bN2bM1	2	4%

T4bN3bMx	2	4%
T4bN3bMo	1	2%
Postoperative		
pT2N0Mx	1	2%
pT2NxM0	1	2%
pT3N0M1	1	2%
pT3N1MO	1	2%
pT3N2bM0	1	2%
pT3N2cM0	1	2%
pT4N2bM0	1	2%
pT4aN1M0	1	2%
HYPOPHARYNX		
T2N3bMO	1	2%
LARYNX		
T2N2bM0	1	2%
T3N0M1	1	2%
T3N3bM0	1	2%
T4aN0M0	1	2%
T4aN3bM1	1	2%
T4bN3bM0	1	2%
OROPHARYNX		
T3N2MO	1	2%
T3N2bM0	1	2%

Table 01: The above table

shows the distribution of study subjects according to the stage of disease. The majority of the study participants were diagnosed with oral cavity cancer, which accounted for the most diverse and frequent staging patterns among all cancer subsites included in the study.

Within the oral cavity cancer group, the most common individual stage observed was T4aN1M0, present in 4 (8.0%) participants. This was followed by several other advanced stages such as T4aN0M0, T4aN1Mx, T4aN1M1, T4aN2cMx, and T4bN1M1, each seen in 2 (4.0%) participants. Additionally, stages such as T3N2bM0, T3N3bM0, T4aN0Mx, T4aN2M0, T4aN2cM0, T4aN3bMx, T4aN3bM0, T4bN0M0, T4bN2bMx, T4bN2bM1, T4bN3bMx, and T4bN3bM0 were each seen in 1 (2.0%) participant, reflecting a wide spectrum of advanced disease presentation. Overall, oral cavity cancers accounted for more than 60% of the cases in the study, highlighting it as the predominant site.

A significant proportion of the study population (8 participants; 16.0%) were recorded in the postoperative staging group. These included a variety of postsurgical stages such as pT2N0Mx, pT2NxM0, pT3N0M1, pT3N1M0, pT3N2bM0, pT3N2cM0, pT4N2bM0, and pT4aN1M0, with each stage being represented by 1 (2.0%) subject. These cases indicate the diversity in post - surgical pathological staging among patients who underwent treatment before enrolment or staging documentation.

Cancers of the larynx were recorded in 6 (12.0%) participants, with stages such as T2N2bM0, T3N0M1, T3N3bM0, T4aN0M0, T4aN3bM1, and T4bN3bM0, each stage being seen in 1 (2.0%) participant. Similarly, oropharyngeal cancers were found in 2 (4.0%) participants, with one subject each diagnosed at T3N2M0 and T3N2bM0 stages. Hypopharyngeal cancer was recorded in 1 (2.0%) participant at T2N3bM0 stage.

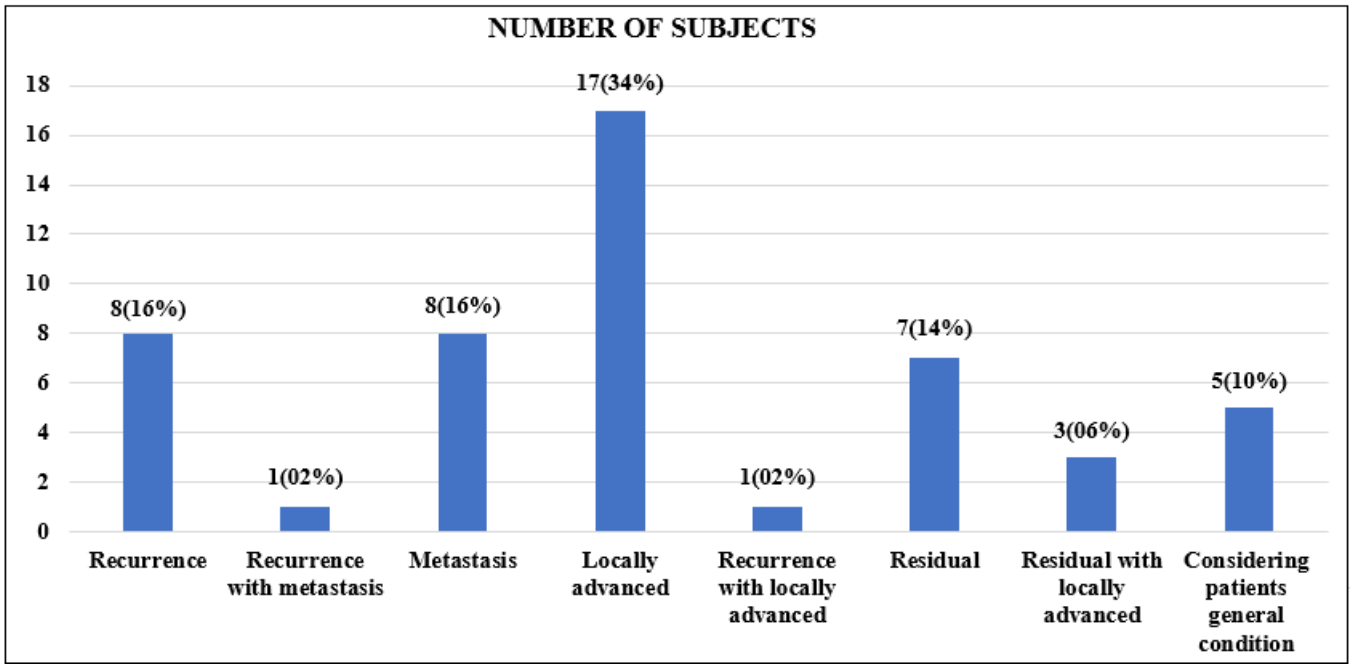

Figure 4: Distribution of study subjects according to Recurrence or Metastasis

Figure 04: The figure shows the distribution of study subjects based on recurrence, metastasis, and disease status. Among the 50 subjects, 17 (34%) had locally advanced disease, while 8 (16%) each had recurrence and metastasis. Recurrence with metastasis and recurrence with locally advanced disease were seen in 1 (2%) participant each. Residual disease was present in 7 (14%) subjects, with 3 (6%) having residual disease along with locally advanced features. Additionally, 5 (10%) cases were classified based on the general condition of the patient. This indicates a high proportion of advanced and recurrent disease in the study population.

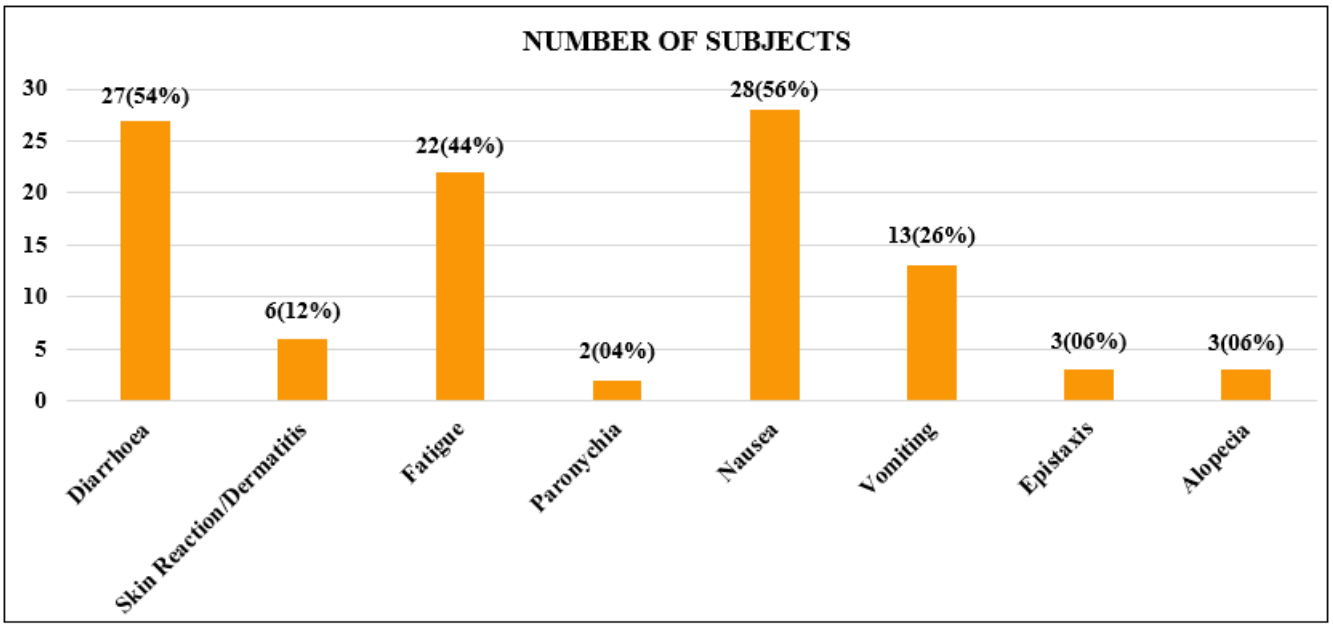

Figure 5: Distribution of study subjects according to Adverse Events
*Multiple Choice

Figure 06: The above figure shows the distribution of adverse events among study subjects. The most common adverse events were nausea in 28 (56%) and diarrhoea in 27 (54%) study subjects. Fatigue was reported in 22 (44%) participants, followed by vomiting in 13 (26%). Skin reactions or dermatitis occurred in 6 (12%) subjects. Less common adverse events included epistaxis and alopecia, each affecting 3 (6%) participants, and paronychia in 2 (4%) study subjects.

Table 2: Distribution of study subjects according to Grades of adverse events

Adverse Events	Grade		
	Grade 1	Grade 2	Grade 3
Diarrhoea	13 (26)	10 (20)	04 (08)
Skin Reaction/ Dermatitis	05 (10)	01 (02)	0
Fatigue	12 (24)	09 (18)	01 (02)
Paronychia	02 (04)	0	0
Nausea	17 (34)	11 (22)	0
Vomiting	10 (20)	03 (06)	0
Epistaxis	03 (06)	0	0
Alopecia	03 (06)	0	0

Table 02: The above table shows the distribution of adverse events among study subjects according to severity grades. The most common adverse event was diarrhoea, reported in 13 (26.0%) subjects as Grade 1, 10 (20.0%) as Grade 2, and 4 (8.0%) as Grade 3. Nausea was observed in 17 (34.0%) participants as Grade 1 and 11 (22.0%) as Grade 2, with no Grade 3 cases. Fatigue was reported as Grade 1 in 12 (24.0%) subjects, Grade 2 in 9 (18.0%), and Grade 3 in 1 (2.0%). Vomiting occurred as

Grade 1 in 10 (20.0%) and Grade 2 in 3 (6.0%) subjects, with no Grade 3 events. Skin reaction/dermatitis was mainly mild, occurring in 5 (10.0%) subjects as Grade 1 and 1 (2.0%) as Grade 2, with no severe cases reported. Less frequent adverse events included paronychia, epistaxis, and alopecia, all observed only as Grade 1 in a small number of subjects.

PFS in months

PFS in Months	No of Patients	Percentage
1 - 3	18	36%
4 - 6	25	50%
7 - 10	7	14%

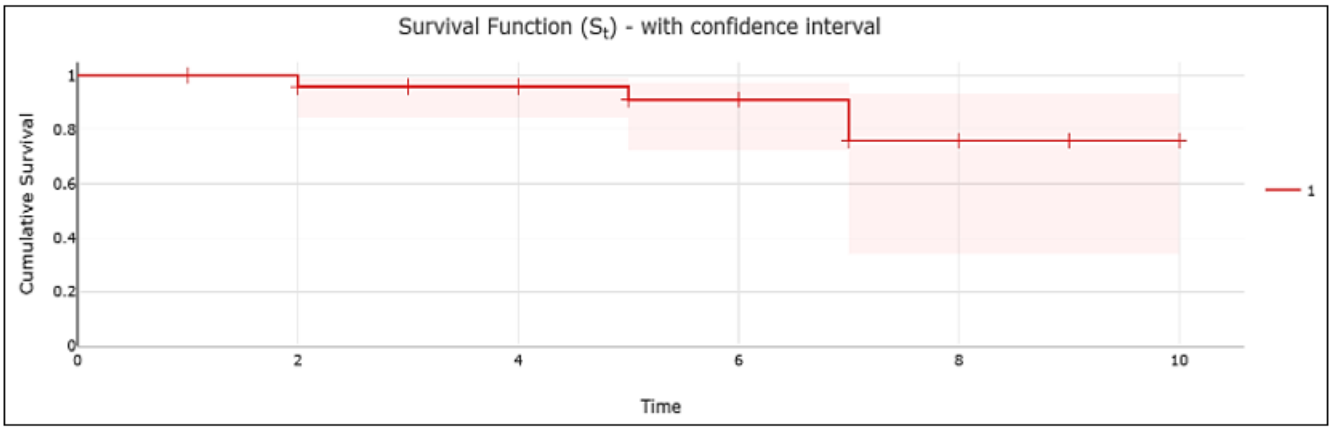

Figure 7: Kaplan Meier Survival Analysis

Figure 07 shows the Kaplan - Meier survival function (St) for the group treated with Afatinib, depicted by the red curve. The curve never drops to 0.5 (50%) on the Y - axis throughout the observed follow - up period. This indicates that the median progression - free survival (PFS) was not reached, meaning that more than 50% of patients remained progression - free at the time of the last follow - up.

According to study, average progression free survival is 5.1 months.

4. Discussion

In the present study, the mean age group of the study subjects was 54.24 ±2.14 years. Similarly, study done by **Burtness et al. [4] (2019)** showed that the mean age group of the study subjects was 58 ±8.4 years. In our study, 76.0% of the study subjects were male and 24.0% were female. Similarly in a study done by **Marret et al. [5] (2023)** showed that 78.0% of the study subjects were male and 22.0% were female and study done by **Burtness et al. [4] (2019)** showed that 85.2% of the study subjects were male and 14.8% were female.

The present study shows that 50.0% of the study subjects were classified as Grade 2 and 24.0% in Grade 1 and it is similar to study done by **Burtness et al. ([4]) (2019)** where 35% of the study participants had an ECOG grade of 1 but in contrast to study done by **Guo et al. ([2]) (2019)** where 79% of the study participants had an ECOG grade of 1.

In this study, the site of primary tumour was oral cavity in 66.0% of the study subjects, followed by hypopharynx in 14.0% of the study subjects and oropharynx in 4.0% of the study subjects. Study done by **Marret et al. ([5]) (2023)** showed that the site of primary tumour was oral cavity in 63.0% of the study subjects, followed by oropharynx in 27.0% of the study subjects and hypopharynx in 10.0% of the study subjects and study done by **Burtness et al. ([4]) (2019)** showed that the site of primary tumour was oropharynx in 52.6% of the study subjects, followed by hypopharynx in 20.7% of the study subjects and oral cavity in 8.5% of the study subjects.

The present study showed 34% had locally advanced disease, while 16% each had recurrence and metastasis. **Guo et al. ([2]) (2019)** showed that 50% had locally advanced disease, while 8% had metastasis.

In our study, the most common adverse events were nausea in 56.0% and diarrhoea in 54.0% of the study subjects. Fatigue was reported in 44.0% of the study participants. Study done by **Haddad et al. [3] (2019)** showed that 87.0 % of the study participants had diarrhoea as the most common adverse events, followed by 84.0% of the study participants had rash/acne and 55.0% of the study participants had stomatitis.

This study showed that most adverse events were of mild to moderate severity (Grades 1 and 2), with Grade 3 events being rare and limited to diarrhoea (8%) and fatigue (2%). No Grade 3 or higher events were reported for other toxicities. Our study was in contrast to study done by **Burtness et al. ([4]) (2019)** where the most common grade 3 to 4 treatment - related AEs with afatinib were rash or acne in 14.8%, diarrhoea in 7.8%, and stomatitis in 13.4% of the study participants.

In our study, more than 50% of patients remained progression - free at the time of the last follow - up and average progression free survival is 5.1 months. Study done by **Burtness et al. [4] (2019)** showed that the Median PFS was 43.4 months (95% CI, 37.4 months to not estimated) and study done by **Haddad et al. [3] (2019)** showed that the Median PFS was 10.8 months (95% CI, 8.2 months to 12.9 months).

5. Conclusion

Afatinib is a treatment of choice, administered as a subsequent line of therapy in patients with recurrent, unresectable, or metastatic locally advanced head and neck squamous cell carcinoma (HNSCC) following progression on or after platinum - based chemotherapy, demonstrated a manageable toxicity profile. The most commonly reported adverse events were diarrhoea, nausea, and fatigue, predominantly of Grade 1 or 2 severity. Grade 3 toxicities were infrequent and controllable with appropriate supportive measures. Also, the Afatinib showed a modest clinical benefit, with a longer progression - free survival of 5.1 months (PFS).

Conflict of Interest

The authors declare no conflict of interest

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